

Low urine pH predicts new onset of diabetes mellitus during a 10-year period in men: BOREAS-DM1 study

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ABSTRACT

Aims/Introduction: A low level of urine pH (U-pH) has been reported to be associated with metabolic disorders. However, the relationship between the incidence of diabetes mellitus and U-pH has not yet been fully addressed.

Materials and Methods: We investigated the relationship between U-pH and the development of diabetes mellitus during a 10-year period in a general population of individuals who received annual health examinations in 2006 ($n = 28,990$). After exclusion of individuals with missing data, and those with diabetes mellitus and/or chronic kidney disease at baseline, a total of 12,476 individuals (men/women: 8,027/4,449) who received health examinations at least once during the period from 2007 to 2016 were recruited. The recruited individuals were divided into four groups according to their U-pH levels: groups of U-pH ≤ 5.0 , 5.5, 6.0 and ≥ 6.5 .

Results: During a 10-year period, 521 men (6.5%) and 132 women (3.0%) had new onset of diabetes mellitus. The cumulative incidence of diabetes mellitus was 7.5% (men/women: 9.3%/4.4%) per 100 person-years. The hazard ratios (HRs) in the U-pH ≤ 5.0 (HR 1.93) and U-pH 5.5 groups (HR 1.46) were significantly higher than that in the U-pH ≥ 6.5 group as a reference for men, but not for women. After adjustment of age, obesity, fasting glucose, smoking and alcohol drinking habits, family history of diabetes mellitus, and use of drugs for hypertension and dyslipidemia, HR in the U-pH ≤ 5.0 group (HR 1.39) was significantly higher than that in the U-pH ≥ 6.5 group for men, but not for women.

Conclusions: Low U-pH predicts new onset of diabetes mellitus in a general population of men.

INTRODUCTION

Diabetes mellitus is a critical issue, as it compromises healthy longevity by multiple complications, including atherosclerotic cardiovascular disease and diabetic nephropathy^{1,2}. The prevalence of diabetes mellitus is continuously increasing worldwide as a result of changes in lifestyle, such as eating habits and exercise³. Therefore, it is important to identify individuals at high risk for new onset of diabetes mellitus and to carry out

appropriate intervention, such as dietary advice and exercise encouragement, at a stage before the onset of diabetes mellitus⁴.

In the body, acidic substances are constantly produced by dietary components or cellular metabolism, and are excreted from the body through the lungs and kidneys to maintain homeostasis⁵. Volatile acids are loaded as CO₂ by cellular aerobic metabolism and are excreted by pulmonary respiration⁵. The amount of volatile acids metabolized and excreted in the body is approximately 15,000 mEq/day⁶. In contrast, non-volatile acids, such as sulfuric acid, phosphoric acid and lactic acid, are loaded by the diet and cell metabolism, and are excreted

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from the kidneys as urine^{7,8}. The amount of non-volatile acids excreted from the body is approximately 1 mEq/kg/day⁹, and acid loading in urine results in lowered urine pH (U-pH). Therefore, U-pH is an index of acid loading in the body.

It has been shown that U-pH is inversely correlated with bodyweight and body mass index (BMI)¹⁰⁻¹². A low level of U-pH has also been reported to be associated with metabolic disorders, such as metabolic syndrome^{13,14}, insulin resistance^{15,16}, impaired glucose tolerance¹⁷, diabetes mellitus¹⁸ and non-alcoholic fatty liver disease^{19,20}. In a longitudinal analysis, a low level of U-pH was shown to be a risk factor for new onset of metabolic syndrome in a 5-year period²¹. Furthermore, logistic regression analysis in a cohort study of 3,119 men showed that the risk of development of diabetes mellitus during a 5-year period was significantly higher in men with U-pH ≤ 5.0 than in men with U-pH ≥ 6.5 (odds ratio 2.69)²². However, whether such a relationship between U-pH and new onset of diabetes mellitus exists in women and in other large cohorts has not yet been fully investigated. Therefore, we investigated the relationship between basal levels of U-pH and new onset of diabetes mellitus during a 10-year period in a general population using a Cox proportional hazards analysis divided into groups by sex.

METHODS

The present study was carried out as a project of the Broad-range Organization for RENal, Arterial and cardiac studies by Sapporo Medical University Affiliates (BOREAS) investigators. The study was a retrospective analysis of data in a prospectively followed cohort designed as the BOREAS-DM1 study. The study conformed to the principles outlined in the Declaration of Helsinki, and was carried out with the approval of the institutional ethical committee of Sapporo Medical University (Number: 29-2-64). Written informed consent was obtained from all of the participants.

Study participants and clinical end-point

All of the individuals who received annual health examinations at Keijinkai Maruyama Clinic, Sapporo, Japan, in 2006 were enrolled in this registry ($n = 28,990$). A flow chart of the study participants is shown in Figure 1. Prespecified exclusion criteria were the absence of data for U-pH, urinary protein, serum creatinine, fasting glucose and hemoglobin A1c (HbA1c) at baseline, and diagnosis of diabetes mellitus and/or chronic kidney disease at baseline. After exclusion, a total of 12,476 individuals (men/women: 8,027/4,449) who received health examinations at least once in the period from 2007 to 2016 were recruited in the present study. The clinical end-point was the development of diabetes mellitus. The use of antidiabetic drugs during a 10-year follow-up period was checked in annual health checkups.

Measurement

Medical examinations, blood pressure measurements, and samplings of urine and blood were carried out after an overnight

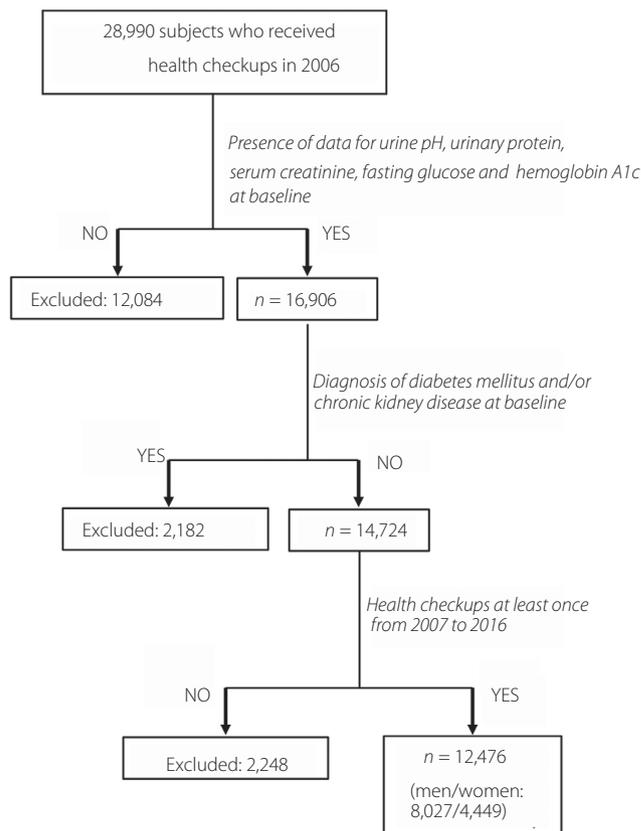


Figure 1 | Flow chart of the selected study participants. Among 28,990 participants enrolled in 2006, a total of 12,476 participants (men/women: 8,027/4,449) were finally recruited for analyses in the present study.

fast. U-pH and urinary protein were examined by the dipstick method. Body height and weight were measured in light clothing without shoes, and BMI was calculated as bodyweight in kilograms divided by height in meters squared. HbA1c level was presented as National Glycohemoglobin Standardization Program equivalent value. As an indicator of renal function, estimated glomerular filtration rate (eGFR) was calculated from data for serum creatinine, age and sex using the following equation: $eGFR \text{ (mL/min/1.73 m}^2\text{)} = 194 \times \text{serum creatinine}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ (if female)²³. A self-administered questionnaire survey was carried out to obtain information on smoking habit, alcohol drinking habit, family history of diabetes mellitus, and use of drugs for diabetes mellitus, hypertension and dyslipidemia. Obesity was defined as BMI ≥ 25 kg/m², and chronic kidney disease was defined as eGFR < 60 mL/min/1.73 m² or positive for urinary protein. Diabetes mellitus was diagnosed in accordance with the guidelines of the American Diabetes Association²⁴: fasting glucose ≥ 126 mg/dL, HbA1c $\geq 6.5\%$ or self-reported use of antidiabetic drugs.

Statistical analysis

Numeric variables are expressed as means \pm standard deviation for parameters with normal distributions and as medians (interquartile ranges) for parameters with skewed distributions. The distribution of each parameter was tested for its normality using the Shapiro–Wilk *W*-test. Clinical parameters were separated by men and women, and each sex group was divided into four subgroups according to baseline U-pH levels: groups of U-pH ≤ 5.0 , 5.5, 6.0 and ≥ 6.5 . Comparison between two groups was carried out with Student's *t*-test for parametric parameters, and with Mann–Whitney's *U*-test for non-parametric parameters. Intergroup differences in percentages of demographic parameters were examined by the χ^2 -test. One-way analysis of variance was used for detecting significant differences between data in multiple groups. Intergroup differences in survival rates were examined by log-rank tests of Kaplan–Meier curves. The hazard ratio (HR) and 95% confidence interval (CI) for the development of diabetes mellitus as a clinical end-point were calculated by using a Cox proportional hazards model with adjustment of confounders, including age, obesity, fasting glucose (≥ 100 mg/dL), smoking habit, alcohol drinking habit, family history of diabetes mellitus, and use of drugs for hypertension and dyslipidemia at baseline. Each parameter of liver function, including aspartate aminotransferase, alanine aminotransferase and γ -glutamyl transpeptidase, was also incorporated as a covariate in additional Cox proportional hazards models. A *P*-value of <0.05 was considered statistically significant. All data were analyzed by using EZR software (Saitama, Japan)²⁵.

RESULTS

Characteristics of the study participants

Characteristics of the recruited and excluded individuals are shown in Table S1. As individuals with diabetes mellitus and/or chronic kidney disease at baseline were excluded, the excluded individuals had significantly higher levels of fasting glucose and HbA1c, and lower levels of eGFR than did the recruited individuals. Demographic parameters and metabolic profiles of the recruited individuals are summarized in Table 1. Women had significantly lower BMI, lower blood pressure, lower levels of albumin, uric acid, fasting glucose, HbA1c, aspartate aminotransferase, alanine aminotransferase, γ -glutamyl transpeptidase, total cholesterol, low-density lipoprotein cholesterol and triglycerides, and higher levels of eGFR, high-density lipoprotein cholesterol and U-pH than did men. The frequencies of obesity and habits of smoking and alcohol drinking were significantly lower in women than in men.

The recruited participants were divided into four groups according to their U-pH levels: groups of U-pH ≤ 5.0 , 5.5, 6.0 and ≥ 6.5 . Basal characteristics of men and women in the four groups at baseline are shown in Table 2. There were significant differences in BMI, presence of obesity, and levels of fasting glucose and HbA1c in the four groups of men, but there were no significant differences in the four groups of women. Men in

Table 1 | Characteristics of the recruited participants

	Total <i>n</i> = 12,476	Men <i>n</i> = 8,027	Women <i>n</i> = 4,449	<i>P</i>
Age (years)	47 \pm 9	48 \pm 9	47 \pm 9	<0.001
Body mass index	23.1 \pm 3.3	23.9 \pm 3.0	21.6 \pm 3.2	<0.001
Obesity	3,780 (30.3)	3,055 (38.1)	725 (16.3)	<0.001
Systolic blood pressure (mmHg)	116 \pm 16	119 \pm 15	110 \pm 16	<0.001
Diastolic blood pressure (mmHg)	74 \pm 11	77 \pm 10	69 \pm 10	<0.001
Smoking habit	4,362 (35.8)	3,532 (45.1)	830 (19.1)	<0.001
Alcohol drinking habit	3,274 (26.2)	2,742 (34.2)	532 (12.0)	<0.001
Family history of DM	2,174 (17.4)	1,270 (15.8)	904 (20.3)	<0.001
Medications				
Antihypertensive drugs	714 (9.9)	809 (10.1)	299 (6.7)	<0.001
Antidyslipidemic drugs	1,108 (8.9)	315 (3.9)	171 (3.8)	0.836
Biochemical data				
Albumin (g/dL)	4.3 \pm 0.2	4.4 \pm 0.2	4.3 \pm 0.2	<0.001
eGFR (mL/min/1.73m ²)	85 \pm 13	84 \pm 12	87 \pm 14	<0.001
Uric acid (mg/dL)	5.4 \pm 1.4	6.0 \pm 1.2	4.3 \pm 0.9	<0.001
Fasting glucose (mg/dL)	89 \pm 9	91 \pm 9	86 \pm 8	<0.001
HbA1c (%)	5.2 \pm 0.3	5.2 \pm 0.3	5.1 \pm 0.3	<0.001
AST (U/L)	21 (18–26)	22 (19–28)	19 (16–22)	<0.001
ALT (U/L)	20 (15–30)	25 (18–36)	15 (12–20)	<0.001
γ GTP (U/L)	30 (19–55)	62 (27–72)	18 (14–26)	<0.001
Total cholesterol (mg/dL)	204 \pm 33	205 \pm 33	203 \pm 33	0.052
LDL cholesterol (mg/dL)	121 \pm 30	123 \pm 30	118 \pm 30	<0.001
HDL cholesterol (mg/dL)	61 \pm 15	56 \pm 14	69 \pm 15	<0.001
Triglycerides (mg/dL)	91 (63–135)	109 (77–157)	67 (50–93)	<0.001
Urine pH	5.9 \pm 0.7	5.9 \pm 0.7	6.0 \pm 0.8	<0.001

Variables are expressed as number (%), mean \pm standard deviation or median (interquartile ranges). †Obesity was defined as body mass index ≥ 25 . γ GTP, gamma glutamyl transpeptidase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

the low U-pH groups tended to have higher BMI, higher frequency of obesity and higher level of fasting glucose than did men in the high U-pH groups.

Cumulative incidence for new onset of diabetes mellitus during the follow-up period

The mean follow-up period was 6.8 years (range 1–10 years), and follow-up summation was 84,808 (men/women: 54,634/30,174) person-years. Among the 12,476 recruited participants,

Table 2 | Characteristics of the participants divided by urine pH at baseline

	U-pH ≤ 5.0	U-pH = 5.5	U-pH = 6.0	U-pH ≥ 6.5	P
<i>n</i>					
Men	1,610	2,442	1,675	2,300	–
Women	987	1,171	814	1,477	–
Age (years)					
Men	50 \pm 8	47 \pm 9	47 \pm 9	48 \pm 10	<0.001
Women	48 \pm 9	46 \pm 9	47 \pm 10	48 \pm 9	<0.001
Body mass index					
Men	24.2 \pm 3.1	23.8 \pm 3.1	23.8 \pm 3.0	23.6 \pm 2.9	<0.001
Women	21.5 \pm 3.2	21.6 \pm 3.3	21.6 \pm 3.4	21.7 \pm 3.1	0.568
Obesity [†]					
Men	713 (44.3)	916 (37.5)	630 (37.6)	796 (34.6)	<0.001
Women	155 (15.7)	203 (17.3)	134 (16.5)	233 (15.8)	0.684
Fasting glucose (mg/dL)					
Men	92 \pm 10	91 \pm 9	91 \pm 8	90 \pm 8	<0.001
Women	86 \pm 8	86 \pm 8	86 \pm 8	85 \pm 8	0.510
HbA1c (%)					
Men	5.3 \pm 0.4	5.2 \pm 0.3	5.2 \pm 0.3	5.2 \pm 0.3	<0.001
Women	5.2 \pm 0.3	5.1 \pm 0.3	5.1 \pm 0.3	5.2 \pm 0.3	0.002

Variables are expressed as number (%) or mean \pm standard deviation.

[†]Obesity was defined as body mass index ≥ 25 . HbA1c, hemoglobin A1c; U-pH, urine pH.

521 men (6.5%) and 132 women (3.0%) had new onset of diabetes mellitus during a 10-year period. The cumulative incidence of new onset of diabetes mellitus was 7.5% (men/women: 9.3%/4.4%, 95% CI 7.0–8.1) per 100 person-years.

Impact of baseline U-pH on the clinical endpoint during a 10-year follow-up period

Kaplan–Meier survival curves showed that there was a significant intergroup difference in the cumulative incidence of new onset of diabetes mellitus for men, but not for women (Figure 2). Cox proportional hazards analysis for new onset of diabetes mellitus during a 10-year follow-up period showed that HRs in the U-pH ≤ 5.0 (HR 1.93) and U-pH 5.5 groups (HR 1.46) were significantly higher than that in the U-pH ≥ 6.5 group as a reference for men (Table 3). After adjustment of age, obesity and fasting glucose (model 1), HRs in the U-pH ≤ 5.0 (HR 1.52) and U-pH 5.5 groups (HR: 1.33) were significantly higher than that in the U-pH ≥ 6.5 group for men. After adjustment of age, obesity, fasting glucose, smoking and alcohol drinking habits, family history of diabetes mellitus, and the use of drugs for hypertension and dyslipidemia (model 2), HR in the U-pH ≤ 5.0 group (HR 1.39) was still significantly higher than that in the U-pH ≥ 6.5 group as a reference for men. When each parameter of liver function, including aspartate aminotransferase, alanine aminotransferase and γ -glutamyl transpeptidase, was additionally incorporated as a covariate, HRs in the U-pH ≤ 5.0 group were still significantly higher than those in the U-pH ≥ 6.5 group as a reference for men (Table S2). In women, there was no significant difference between HRs of the four U-pH groups (Table 4, Table S3).

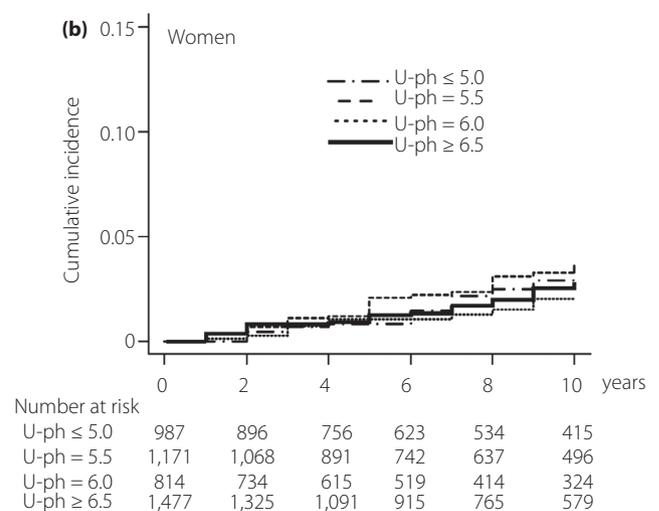
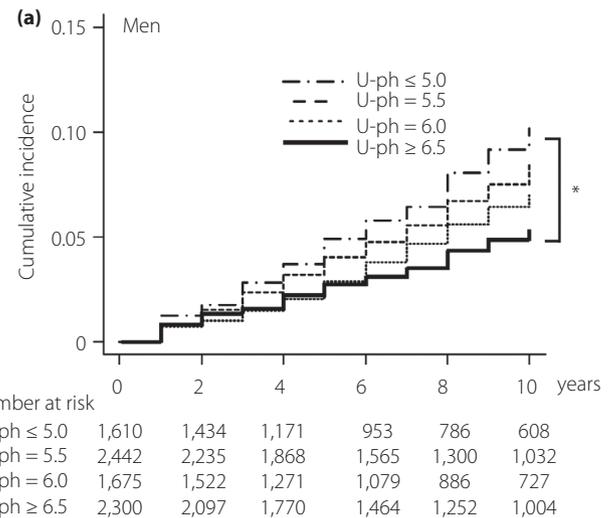


Figure 2 | Cumulative incidence of diabetes mellitus in four groups of urine pH at baseline. (a) Kaplan–Meier survival curve analyses for cumulative incidence of diabetes mellitus in men ($n = 8,027$) with baseline urine pH (U-pH) ≤ 5.0 ($n = 1,610$), 5.5 ($n = 2,442$), 6.0 ($n = 1,675$) and ≥ 6.5 ($n = 2,300$). (b) Kaplan–Meier survival curve analyses for cumulative incidence of diabetes mellitus in women ($n = 4,449$) with baseline urine pH (U-pH) ≤ 5.0 ($n = 987$), 5.5 ($n = 1,171$), 6.0 ($n = 814$) and ≥ 6.5 ($n = 1,477$). * $P < 0.001$.

DISCUSSION

The present study using a large number of participants ($n = 12,476$, men/women: 8,027/4,449) who received an annual health checkup showed that a low level of U-pH was significantly associated with the risk of diabetes mellitus development during a 10-year period in men who had no diabetes mellitus and/or chronic kidney disease at baseline. It has been reported that a low level of U-pH is associated with several metabolic disorders^{13–22}. A previous study showed an association between low U-pH and new onset of diabetes mellitus in men²², similar to results of the present study. The risk of diabetes mellitus

Table 3 | Cox proportional hazard analyses for new onset of diabetes mellitus in men

	Unadjusted		Model 1		Model 2	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
U-pH ≤ 5.0	1.93 (1.54–2.52)	<0.001	1.52 (1.18–1.95)	<0.001	1.39 (1.07–1.79)	0.001
U-pH 5.5	1.46 (1.15–1.85)	0.001	1.33 (1.04–1.69)	0.002	1.17 (0.91–1.50)	0.197
U-pH 6.0	1.18 (0.89–1.55)	0.231	1.09 (0.83–1.44)	0.504	1.05 (0.79–1.39)	0.711
U-pH ≥ 6.5	Reference	–	Reference	–	Reference	–
Age (per 10 years)	–	–	1.17 (1.06–1.30)	<0.001	1.18 (1.06–1.32)	<0.001
Obesity [†]	–	–	1.91 (1.60–2.29)	<0.001	1.76 (1.46–2.12)	<0.001
Fasting glucose (≥ 100 mg/dL)	–	–	9.7 (8.0–11.7)	<0.001	9.7 (8.0–11.8)	<0.001
Smoking habit	–	–	–	–	1.76 (1.46–2.11)	<0.001
Alcohol drinking habit	–	–	–	–	0.83 (0.68–1.05)	0.140
Family history of DM	–	–	–	–	1.41 (1.15–1.73)	<0.001
Antihypertensive drugs	–	–	–	–	1.20 (0.93–1.54)	0.145
Antidyslipidemic drugs	–	–	–	–	1.63 (1.18–2.25)	<0.001
	(AIC 8,960)		(AIC 8,195)		(AIC 7,788)	

$n = 8,027$. [†]Obesity was defined as body mass index ≥ 25 . AIC, Akaike's information criterion; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; U-pH, urine pH.

Table 4 | Cox proportional hazards analyses for new onset of diabetes mellitus in women

	Unadjusted		Model 1		Model 2	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
U-pH ≤ 5.0	1.18 (0.73–1.90)	0.481	1.03 (0.64–1.66)	0.888	1.02 (0.62–1.67)	0.930
U-pH 5.5	1.25 (0.80–1.95)	0.322	1.11 (0.70–1.75)	0.635	1.17 (0.74–1.86)	0.494
U-pH 6.0	1.08 (0.64–1.81)	0.762	0.99 (0.59–1.67)	0.987	1.01 (0.60–1.72)	0.952
U-pH ≥ 6.5	Reference	–	Reference	–	Reference	–
Age (per 10 years)	–	–	1.31 (1.08–1.58)	0.004	1.35 (1.10–1.66)	0.004
Obesity [†]	–	–	2.61 (1.82–3.73)	<0.001	2.61 (1.80–3.77)	<0.001
Fasting glucose (≥ 100 mg/dL)	–	–	13.3 (9.2–19.0)	<0.001	12.4 (8.5–17.9)	<0.001
Smoking habit	–	–	–	–	1.38 (0.89–2.15)	0.142
Alcohol drinking habit	–	–	–	–	0.93 (0.54–1.60)	0.797
Family history of DM	–	–	–	–	1.73 (1.18–2.54)	0.004
Antihypertensive drugs	–	–	–	–	1.20 (0.72–2.00)	0.464
Antidyslipidemic drugs	–	–	–	–	1.65 (0.92–9.75)	0.091
	(AIC 2,104)		(AIC 1,871)		(AIC 1,802)	

$n = 4,449$. [†]Obesity was defined as body mass index ≥ 25 . AIC, Akaike's information criterion; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; U-pH, urine pH.

development in men with U-pH ≤ 5.0 (odds ratio 2.69; participants with U-pH ≥ 6.5 as a reference) in the previous study²² seemed to be higher than that in the present study (HR 1.93 in the unadjusted model). In the previous study²², the cumulative incidence of diabetes mellitus was not analyzed, and only men ($n = 3,119$) were examined for a 5-year period. In the present study, we included more than a twofold larger number of men and longer follow-up period, and showed a significant association of low U-pH with the risk of new-onset diabetes mellitus in men after adjustment of age, obesity, fasting glucose, liver function, smoking and alcohol drinking habits, family history of diabetes mellitus, and the use of drugs for hypertension and dyslipidemia. In addition, we found a significant sex difference

in the relationship between U-pH and the risk of new-onset diabetes mellitus: there was no significant association between U-pH and new onset of diabetes mellitus during a 10-year follow up in women.

In the body, non-volatile acidic substances are constantly loaded by the diet and cell metabolism, and H⁺ is excreted from the kidneys with bicarbonate ions, titrated acids (such as phosphate) and ammonia produced from glutamine in the proximal tubule^{5,7,26,27}. Therefore, net acid excretion²⁸ and dietary acid load^{29,30} are associated with low U-pH level. It has been reported that accumulation of non-volatile acids is associated with metabolic abnormalities, including impaired glucose tolerance, insulin resistance and diabetes mellitus^{12,31–34}. Insulin

is directly involved in the excretion of H^+ from the kidneys through the activation of Na^+/H^+ exchanger 3^{26,27}, suggesting that hyperinsulinemia as a result of insulin resistance decreases U-pH level. In addition, renal production of ammonia, which titrates the acid–base balance, is impaired in a condition of insulin resistance^{13–16,35,36}. Furthermore, the ratio of urinary ammonium to total urinary acid excretion and net acid excretion by ammonium from the kidneys were shown to be reduced in patients with diabetes mellitus¹⁸. These findings suggest that metabolic disorders derived from insulin resistance cause acid accumulation in the body, resulting in a low U-pH level. Conversely, low interstitial fluid pH attenuates the insulin signaling pathway and increases insulin resistance^{37–40}. As U-pH is positively correlated with body fluid pH⁴¹, U-pH level would be a surrogate marker of insulin resistance in the body. In fact, we found that low U-pH was associated with obesity and high fasting glucose in men who had no diabetes mellitus (Table 2).

In the present study, an association between low U-pH and new onset of diabetes mellitus was found in men, but not in women. U-pH has been reported to be higher in women than in men^{42,43}, which was confirmed in the present study. The rate and amount of urine excretion of citrate, which has a basic property, were reported to be significantly higher in women than in men in a condition of hospitalization with a restricted diet⁴⁴, suggesting that women are protected from lowering of U-pH level. In fact, a cross-sectional study using a large number of Korean participants ($n = 22,297$, men/women: 13,895/8,402) showed that low U-pH was associated with obesity in men, but not in women⁴⁵. Another cross-sectional study using apparently healthy Japanese adults ($n = 3,629$, men/women: 2,311/1,318) also showed that low U-pH was associated with both high ($\geq 27 \text{ kg/m}^2$) and low ($< 19 \text{ kg/m}^2$) levels of BMI⁴⁶. Taken together, the results suggest that differences in physique, citrate excretion rate and/or dietary preference are involved in the sex difference in the relationship between U-pH and risk for diabetes mellitus.

Another possible reason for the sex difference in the association between low U-pH and new onset of diabetes mellitus is the difference in estrogen levels. It has been reported that estrogen has favorable effects on glucose homeostasis, and protects against hyperglycemia by reducing hepatic glucose production and enhancing glucose transport in skeletal muscle⁴⁷. Therefore, women, especially those before menopause, might be protected from the acid loading-induced risk of diabetes mellitus.

The strong points of the present study were that the study participants were recruited from a large number of individuals in a general population, and that new onset of diabetes mellitus during a 10-year period was examined. However, the present study had some limitations. First, as the present study recruited individuals who received an annual health checkup, the influence of self-selection bias cannot be denied. Relatively, a more healthy population would be included in the recruited individuals, and the results might be underestimated. As the processing

of missing data was based on the listwise method, selection bias was also considered to be a research limitation. Second, only Japanese individuals were recruited in the present study, and it is not clear whether the results apply to other races. Third, there was a possibility of type II error, especially in statistical analyses of women, because the number of women was much smaller than that of men. Fourth, a test paper method using an indicator for U-pH was used instead of an electrode method because of its convenience and cost. The electrode method is thought to be more reliable, but recent studies have shown the accuracy of the test strip method⁴⁸. Fifth, diet, medication and comorbidities including urinary infection, which might affect U-pH, were not evaluated in the present study, although individuals with diabetes mellitus and/or chronic kidney disease at baseline were excluded. Finally, the relationship between change in U-pH and onset of diabetes mellitus was not investigated in the present study, and this relationship needs to be examined in the future.

In conclusion, a low level of U-pH is an independent predictor of the development of diabetes mellitus in men, but not in women. The pathophysiology underlying the association between acid loading in the body and diabetes mellitus development needs to be addressed in future basic and clinical studies.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Characteristics of the recruited and excluded individuals.

Table S2 | Cox proportional hazards analyses for new onset of diabetes mellitus including liver function as a covariate in men.

Table S3 | Cox proportional hazards analyses for new onset of diabetes mellitus including liver function as a covariate in women.